DR. NANCY DAVIDSON: So now we're going to move and think about preoperative therapy with one of the biologics – anti-HER2 agents from Dr. Buzdar from M.D. Anderson.

DR. AMAN BUZDAR: Thank you very much, colleagues. What I am going to do is, in the next few minutes, very briefly review the preoperative biologic therapies in HER2/neu positive patients. The review will include the trastuzumab monotherapy data; concomitant/combination with chemotherapy drug -- mostly Phase 2 studies; as well as limited data from randomized trials. And also I will comment on the initial data regarding the lapatinib in HER2/neu positive patients. I will also try to summarize a number of correlative science studies which were carried out in these trials.

A couple of studies have evaluated the trastuzamab. (I think you have my old slides. They did not update the slides which I had sent.) The trastuzumab has been evaluated in a number of studies as a monotherapy, and this is one study which was carried out by the group at Baylor College of Medicine. They had 35 patients which were included, and patients were treated for three weeks with trastuzumab therapy; and then the biopsy was carried out and clinical response was assessed. At three weeks, 23 percent of the patients had partial response. Correlative laboratory studies demonstrated an increased apoptosis, but there was no change in the EGFR or in HER2 values.

In another study, which had only 11 patients -- these patients were treated for only four weeks. And in this small study, one patient had a complete response, which was nine percent, and pathological partial response was in about 36 percent of the patients. And there was no progression of the patients in this study.

And these were some of the data, which I will quickly skip, and if we look at it, over here, at the apoptosis which the others show, that after week one there was significant change in apoptosis; and if we look at it, there was no significant change in Ki67, p27 and also there was some decrease in cytoplasmic p-MAP kinase in three weeks.

I think they have tried to correlate, and a number of other people have tried to correlate, the genes which may be able to predict pathological complete response in patients who are being treated with trastuzumab and chemotherapy. My bottom line -- which was in the different slide -- but I don't think that, at the present time, we are there where we can identify this information.

This is the study which I was talking about, since the slides are out of order here, that in this 11-patient study in which the trastuzumab was evaluated as a monotherapy -- one patient had a pCR, which was about nine percent, and four patients, which was about 34 percent of the patients, had partial response, and six patients which had a partial -- a minor response.

A number of studies have evaluated trastuzumab with the taxanes or with vinorelbine, or combinations of the drugs. If we look at it over here, the patients which were treated with these type of therapies, on the average, the duration of trastuzumab and chemotherapy was about 12 to 16 weeks. And if we look at the clinical complete remission rate, which is about 30 to 50 percent; but the pathological complete response rates are about 12 to 20 percent.

Some of the studies which have higher pathological complete response rates -- I think their definitions are somewhat different and they do include patients who have small, residual invasive cancer and are classified as a pathCR.

Several studies have included docetaxel with trastuzumab studies, and those are summarized over here. Again, you see the number of patients in these studies and the average duration is about 12 to 18 weeks. Clinical CR rates, again, are fairly high, but if you look at the pathological complete response rate, they are about 12 to 47 percent; and the one which is 47 percent, I think the definition is, again, some of the European definitions where they do include some of the minimal residual invasive disease.

A few studies have included also cis- or carboplatin in this combination with docetaxel; and the trastuzumab therapy is about 12 to 16 weeks. If we look at it, what I just showed you in the previous slide over here, the pathological response… path CR rate and path CR rate over here, it looks to me very similar. So, in my judgment, addition of carbo or cis- platinum in management of HER2/neu positive patients remain to be defined; and it does not seem to add much in increasing the pathological complete response.

And this is very consistent with the BCIRG study, which in metastatic disease, in which docetaxel alone with trastuzamab, versus docetaxel with carboplatin and Herceptin, did not show higher response rate, time to progression, or improvement in survival, although the dose of [docetaxel in the?] monotherapy arm was somewhat higher, and in the carboplatin arm the dose of docetaxel was somewhat lower. But I think if you look at the dose, which was substantially attenuated because 100 per meters squared cannot be given to these patients consistently.

A small number of studies have been carried out in which the patients were initially treated with anthracycline and cyclophosphamide combination, and then they were switched to either taxane with trastuzumab or with, in one study, taxane with gemcitabine. And if we look at it, the duration of the studies again is about 12 to 16 weeks and the pathological complete response rate is about 20 to 30 percent; and one study which had a 70 percent response rate, some patients had persistent residual microscopic invasive disease.

This was a study carried out by NSABP Group in which a very similar study design as we utilized at M.D. Anderson, in which, instead of paclitaxel, Nab-Taxol [nab-paclitaxel] was utilized; and patients got attenuated doses of FEC, which is epirubicin at 75 milligrams. And the total duration of trastuzumab and the chemotherapy, which was taxane and also FEC, for a total of 24 weeks. And the pathological complete response rate was about 59 percent.

Single-agent lapatinib -- there are two studies which I very briefly want to review is:

One is a study which is ongoing across… in Houston, in which patients who are HER2/neu positive -- they are getting monotherapy with lapatanib; and the biopsy is done at baseline and then at these points for six weeks. And, talking to Jenny Chang, the specific aim of the study is, besides looking at the clinical efficacy of the drug, to see some of the gene expression arrays which may predict sensitivity or resistance with this therapy.

And this mammogram, which is kind of… you can maybe see it: there is a huge mass which was present and it subsequently shows regression. I got in verbal communication from Dr. Chang that a number of patients have shown similar, excellent response for a short period of time; and I think this is encouraging, and the role of this drug needs to be further evaluated in this model.

Another study, which was carried out in patients with inflammatory carcinoma of the breast who were HER2/neu positive -- they were given lapatinib for two weeks alone and then they were given lapatinib concomitantly with taxane. And in this study, after 14 weeks of therapy, the pathological complete response rate was about 17 percent.

Now let me briefly talk about our randomized trial in which we evaluated the efficacy of trastuzumab in combination with taxane and with FEC combination. Patients were given concomitantly either trastuzumab throughout, from day one, for 24 weeks, or patients got chemotherapy alone. This study -- after initial efficacy data was available -- the control arm was stopped and additional 22 patients were treated with the chemotherapy and with trastuzumab.

Pre-treatment characteristics of these patients -- three arms, which is the first two arms of the randomized, and the third is an assigned arm which was after we stopped the chemotherapy-alone arm -- these are very similar characteristics.

And the safety data which was, that when we gave the paclitaxel over here, which was given as a 24-hour infusion once in three weeks, there was more myelosuppression and some patients experienced neutropenic fever; but no other immediate(?) toxicity was observed.

And if we look at the patient population which we included in this study, this is what we see it in the average practice -- that you can see that at baseline these patients had hypertension, diabetes, EKG abnormalities -- a small number of patients had valvular changes.

In spite of that, the safety data which you're going to see in the next couple of slides -- that only one patient in the control group, after completing chemotherapy, she developed an acute myocardial infarct, and subsequently had clinical cardiac dysfunction. But none of the other patients had clinical cardiac dysfunction -- although a number of patients, as I will show you, there was a drop in the ejection fraction which was of sub-clinical -- data which you will see.

If we look at the extent of the residual disease -- that extent of the residual disease in patients who got chemotherapy with trastuzumab -- that is, that extent of the residual disease were either very minimal or small-volume disease left, and this will be addressed by Fraser Symmans; because these patients actually tend to do very well in the long run.

And if we look at the pathological complete response rate in our three cohorts of the patients, that in patients who were treated with chemotherapy alone, the pathological complete response rate was about 26 percent, and the patients who were given trastuzumab, the pathCR rate is about 65, or 55 percent in the second cohort.

And another thing which is very important if you look at the other side of the road, where we look at the pathological complete response rate according to the ER and the PR status

-- positive versus negative -- as it has been addressed by a number of other speakers earlier, that patients who are ER positive, actually chemotherapy -- if they are HER2/neu negative and treated with chemotherapy, pathological CR rate in that sub-group of patient population is about five to ten percent.

But over here you see that, even with chemotherapy alone, pathological complete response rate, both in hormone-receptor-positive and hormone-receptor-negative patients is about 25 to 27 percent; and with inclusion of trastuzumab, those pathological complete response rates go up to about approximately 60 percent.

Another thing which we looked at these studies is that, is there a way that we could identify this 60-plus percent of the patients who have no invasive residual disease? Actually, we did ultrasound, mammogram, and all kinds of things on these patients; and the thing which we found is, the clinical assessment of the physician was the best.

I think the MRI, we did not do it at that time -- we did not have the facilities, but now we have the facilities. But clinical evaluation by ultrasound and mammography were not good predicting the patients who had actually clinical -- pathological complete response. As you can see it, in a sizable number of patients who had pathological complete response, there was persistent abnormalities on these imaging studies.

And these are the cardiac data on individual patients -- if you can see it over here -- that we did baseline evaluation after 12 weeks, then at 24 weeks and then, subsequently, after completion of therapy we modified the protocol and these studies were evaluated.

And up to four years, only patient which you can see is in the top one which is the control group -- the patient I described earlier who developed a myocardial infarct. All the other patients do show a small drop in the ejection fraction, but they all remain within the normal range of our lab. And this is just to show you the same data, in this bar graph, that you see a small, modest drop from the baseline all three sub-groups are seeing, but in

the patients who got trastuzamab, there is a drop in the ejection fraction about by five points.

And this is the survival data. If we look at the disease-free survival of this patient population -- these are the first randomized patient population. Now, the median follow-up of these patients is about four years. So far, in the patients who have received trastuzumab with chemotherapy together, all patients are alive, free of disease. Whereas, in the 19 patients which we treated with chemotherapy alone, three patients have developed recurrent disease, and two out of three of those patients have died.

Another large study which is ongoing in NCI-Milan is called the NOAH trial; and the design of that study is shown over here. This study evaluates patients who are locally advanced [including inflammatory] carcinoma, to see if they are HER2/neu positive by FISH. And if they are HER2/neu positive, then they're randomized to get chemotherapy or chemotherapy with trastuzumab concomitantly. And the chemotherapy is AT, then T alone, and then CMF. And the details of chemotherapy are shown over here. AT is the doxorubicin and paclitaxel, and T is then paclitaxel alone, and then later, standard CMF. And the patients who are assigned… are randomized to the trastuzumab arm, they get conventional dose of trastuzumab for a total of one year.

This study has finished accrual as of December 2005 and has 334 patients -- out of those, 99 were HER2/neu negative, so they are assigned to the chemotherapy-alone arm; and about 118 patients are in each arm. And these data -- I think Professor Luca Gianni might like to comment during the discussion. But I think this study is interesting and it will provide very important information about this.

And the last slide which we have -- this is a ACOSOG study which we'll initiate shortly. And the objective of this study is to see what is the best sequence -- whether we can initiate the chemotherapy and give it concomitantly with trastuzumab, or it is safer and

maybe as efficacious if we utilize it during the paclitaxel phase. And this study is going to launch in the next few months. I will stop over here and thank you very much.